Serum Ferritin Concentration and Recurrence of Colorectal Adenoma

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Abstract

Both body iron stores and dietary iron intake have been reported to increase risk of colorectal neoplasms. We assessed whether serum ferritin concentration was associated with recurrence of colorectal adenomas among 733 individuals with baseline determinations of ferritin as part of a multicenter clinical trial of antioxidant supplements for adenoma prevention. All study participants had at least one adenoma removed within 3 months before enrollment, and 269 of them developed one or more adenomas between follow-up colonoscopies conducted 1 and 4 years after enrollment. Baseline serum ferritin concentrations were analyzed both as a log-transformed continuous variable and as a categorical variable, defined as whether iron stores were nonreplete and low (ferritin ≤30 μg/liter), nonreplete and borderline (31–70 μg/liter), replete and adequate (71–160 μg/liter), or replete and high (>160 μg/liter). Analyses were based on multiple logistic regression models, including age, sex, study center, energy, alcohol, fiber, folate, and total fat intake, number of months between colonoscopic examinations, smoking status, and aspirin use. Overall, there was no statistically significant linear association between log ferritin concentration and adenoma recurrence ($P = 0.33$). Risk of adenoma recurrence was modestly increased among participants with ferritin concentrations >70 μg/liter relative to those with lower ferritin (odds ratio, 1.39; 95% confidence interval, 0.96–2.02). This result seemed more pronounced among women than men. Dietary intake of iron and red meat was inversely associated with adenoma recurrence among participants with replete iron stores but not consistently associated among those with nonreplete stores. Our findings suggest that any role of iron stores and dietary iron in influencing risk of colorectal adenoma recurrence is likely complex.

Introduction

Laboratory experiments and epidemiological studies suggest that iron may increase risk of colorectal neoplasia (1). One possible mechanism for this effect is through iron's pro-oxidant properties (2). In addition, iron has been reported to stimulate proliferation of tumor cells (3, 4) in experimental animals, perhaps because it is an essential nutrient for tumor growth (5). In epidemiological studies, both iron stores (6–9) and dietary iron (10) have been associated with increased risk of colorectal cancer. These studies have not shown, however, whether there is a continuous increase in risk associated with iron exposure, or whether there are thresholds for a protective effect of relative iron deficiency or an adverse effect of iron excess. It is also unclear whether the relevant measure of iron is total body iron stores or the amount in the colonic lumen, a reflection of dietary intake and small bowel absorption.

Most colorectal cancers appear to arise from adenomas, and research regarding the association between iron stores and these precursors could help elucidate the role of iron exposure early in the tumorigenic process. Two prior studies, both case-control in design, have examined risk of adenoma in relation to iron stores (6, 11). We used prospective data from a randomized prevention trial to examine the association between serum ferritin concentration as a measure of body iron stores and recurrence of adenomas. In a previous analysis in the same study population, we found an inverse association between dietary iron and adenoma recurrence (12). In the present analyses, we also explored whether iron stores modified the relationship between dietary iron and adenoma risk.

Materials and Methods

Study Population. We based our analyses on data from participants in the Antioxidant Polyp Prevention Study, a multicenter clinical trial of antioxidant supplementation to prevent colorectal adenomas (13). Participants in the trial were identified between December 1984 and June 1988 from colonoscopy reports and pathology logs at six centers: Cleveland Clinic (Cleveland, OH), Dartmouth-Hitchcock Medical Center (Lebanon, NH), Lahey Clinic Medical Center (Burlington, MA), University of California, Los Angeles/Kaiser Sunset (Los Angeles, CA), the University of Iowa (Iowa City, IA), and the University of Minnesota (Minneapolis, MN). All had at least one histologically confirmed adenoma removed within 3 months of study entry and were judged to be free of further polyps based on complete colonoscopy before enrollment. Patients were excluded if they had familial polyposis, a history of invasive colorectal cancer, any malabsorption syndromes, or any conditions that might be worsened by vitamin C or E supplementation, such as renal calculi or thrombophlebitis.

All trial participants gave informed consent and were

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randomly assigned using a two-by-two factorial design to four treatment groups: β-carotene plus placebo, vitamins C and E plus placebo, β-carotene plus vitamins C and E, and placebo only. Two complete follow-up colonoscopies were conducted ~1 year and 4 years after the qualifying colonoscopy. At these follow-up examinations, any raised mucosal lesions were excised, and microscopic slides were sent for review by the study pathologist. Polyps were classified as either neoplastic (adenoma) or nonneoplastic (hyperplastic polyp, lymphoid follicle, or other type of lesion). A total of 751 patients (of 864 randomized) completed the trial and had the year 4 colonoscopy examination. Of the 113 patients who did not complete the study, 44 died, 32 were no longer interested in participating, 19 moved or became too ill to continue, and 18 dropped out for unknown reasons. There was no effect of the study agents on risk of new adenomas (13). In the present analyses, as in our prior report of dietary iron and adenoma recurrence (12), patients found to have one or more adenomas during the interval after the year 1 exam up to and including the year 4 exam were classified as cases, whereas those without adenomas were classified as controls. We did not consider adenomas diagnosed at the year 1 colonoscopy in determining case status because many of these tumors were likely present at the time that patients enrolled in the trial (13). Large and/or multiple adenomas occurred too infrequently to permit an informative analysis.

Measurement of Serum Ferritin. Venous blood was taken at enrollment in mineral-free vacuum tubes. Aliquots of serum were frozen in polypropylene tubes and shipped to the coordinating center at Dartmouth for storage. A blood chemistry panel was performed shortly after receipt of the specimens and included measures of alkaline phosphatase and aspartate aminotransferase. Serum ferritin samples were assayed at the Fox Chase Cancer Center using IMx ferritin assay kits (Abbott Laboratories), which are based on a microparticle enzyme immunoassay. The probe/electrode assembly of the IMx apparatus delivers the sample, diluent, antiferritin alkaline phosphatase conjugate, and antiferritin-coated microparticles to an incubation well. After incubation, an aliquot of reaction mixture is transferred to a glass fiber matrix. The microparticles bind irreversibly to the glass fiber matrix. Unbound material is removed, 4-methylumbelliferyl phosphate is added as substrate, and the microparticle enzyme immunoassay optical assembly is used to measure the fluorescent product against a standard curve computed from six sample calibrators supplied with the kits. Laboratory personnel were blinded to patients' treatment assignments and colonoscopy outcomes.

Questionnaire Data. At enrollment into the trial, patients completed a questionnaire that included information about smoking history and use of vitamin and mineral supplements. Nutrient intake was assessed from a self-administered food frequency questionnaire (14) given before randomization. Patients estimated their frequency of intake and usual portion size over the previous year for >100 food items. Average dietary nutrient intakes per day were calculated based on the nutrient content and reported portion size and frequency of consumption of each food. In addition, a variable representing weekly frequency of red meat consumption was created as a proxy for heme iron, which is much more bioavailable than iron from other sources. The red meat frequency measure was based on reported consumption of hamburger, beef, beef stew, pork, veal/lamb, chili con carne, and mixed dishes with meat. We excluded from our analyses data from 36 patients who reported eating <3 foods a day, skipped >50 foods in the questionnaire, or reported daily caloric intake <500 or >5000 kcal/day.

Data Analysis. Our analyses focused on baseline serum ferritin concentration as a measure of iron stores before the main risk period of the study, the interval after the first (year 1) follow-up colonoscopy up to and including the exit (year 4) colonoscopy. We first tested whether there was a linear relationship between adenoma recurrence and ferritin concentration, analyzed as a log-transformed continuous variable. We then considered risk in relation to estimated iron stores: nonreplete and low (ferritin ≤30 μg/liter), nonreplete and borderline (31–70 μg/liter), replete and adequate (71–160 μg/liter), or replete and high (>160 μg/liter). This categorization scheme is based on recent data regarding ferritin and iron absorption (15) and differs from methods used in previous studies, which usually grouped participants into quartiles or quintiles of ferritin concentration (11, 16). We used a serum ferritin concentration of ≥70 μg/liter to indicate replete iron stores, relying on research suggesting that serum ferritin concentration and iron absorption are closely inversely correlated when ferritin concentration is <70 μg/liter, but that above this level iron absorption is minimal and roughly equal to the estimated rate of loss of iron from the body (15). We posited that effects of dietary iron on adenoma risk would be particularly evident in patients with ferritin concentrations >70 μg/liter because replete iron stores and minimal iron absorption would increase exposure of colonocytes to luminal iron. At ferritin concentrations <70 μg/liter, we hypothesized that there would be only a weak association of iron intake with risk because depleted iron stores and increased intestinal absorption of dietary iron would limit colonocyte exposure to luminal iron.

We used unconditional logistic regression first to test for a linear trend of the continuous, log-transformed ferritin variable and, next, to estimate ORs[2] and 95% CIs for categories of serum ferritin coded as dummy variables. A minimally adjusted model included age, sex, and center. A more fully adjusted model included intake of energy, alcohol, total dietary fiber, folate, and total fat; number of months between the year 1 and exit colonoscopies; smoking status; and aspirin use. Intakes of alcohol, fiber, folate, and fat were energy-adjusted by using the residuals from the regression of the nutrient on caloric intake (17) and categorized into quartiles. Although duration of follow-up was not clearly related to serum ferritin levels in bivariate analyses (data not shown), we included number of months between year 1 and year 4 colonoscopies as a covariate. We tested for linear trend by including an ordinal variable representing the scaled median value for each category in a logistic regression model while controlling for the same covariates listed above. Minimally and fully adjusted models included only those patients not missing information on any of the variables included in the fully adjusted model. Body mass index, vitamin/mineral supplement use, treatment group, and family history of colorectal cancer were not found to be associated with either serum ferritin concentration or adenoma recurrence in bivariate analyses and were not further considered as potential confounders. The distribution of ferritin concentrations differed between women and men; thus, we ran stratified models as well as models with ferritin concentration × sex category interaction terms.

We conducted two additional analyses to account for serum ferritin concentrations that may have been elevated for

[2] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 1 Characteristics of study population by case status and sex ($n = 733$)

	Cases ($n = 269$)	Noncases ($n = 464$)
Mean age ± SD (yr)	61.5 ± 8.3	60.5 ± 8.3
Sex (% male)	81.8	76.7
Dietary intake (mean per day ± SD)		
Energy (kcal)	1999 ± 732	1954 ± 772
Energy from alcohol (kcal)	136 ± 219	93 ± 203
Fiber (g)	14 ± 7	15 ± 8
Folate (mg)	313 ± 149	324 ± 176
Total fat (g)	89 ± 42	85 ± 44
Iron (mg)	13.7 ± 6.0	14.9 ± 7.4
Red meat (servings)	0.5 ± 0.4	0.5 ± 0.4
Smoking status (%)		
Nonsmoker	30.7	34.6
Current smoker	18.0	19.5
Former smoker	51.3	46.0
Aspirin use at baseline (%)	20.1	26.7

Table 2 Distribution of baseline ferritin concentrations by sex and disease status ($n = 733$)

	Women		Men	
	Cases ($n = 49$)	Noncases ($n = 108$)	Cases ($n = 220$)	Noncases ($n = 356$)
Geometric mean ± SD (μg/liter)	82.3 ± 2.3	62.6 ± 2.6	113.6 ± 2.7	113.9 ± 2.8
Median (μg/liter)	92	68	122.5	120.5
Range (μg/liter)	14–654	4–399	4–800	2–853
Ferritin concentration (%)				
0–30 μg/liter	14.3	20.4	9.1	11.0
>30–70 μg/liter	26.5	35.2	16.8	16.3
>70–160 μg/liter	38.8	25.9	35.5	35.1
>160 μg/liter	20.4	18.5	38.6	37.6

Table 3 ORs for adenoma recurrence by serum ferritin concentration ($n = 687$)

Ferritin level (μg/liter)	No. of cases/noncases	Minimally adjusted OR[a] (95% CI)	Fully adjusted OR[b] (95% CI)
0–30	26/57	1.0	1.0
>30–70	46/93	0.98 (0.54–1.78)	1.03 (0.54–1.94)
>70–160	90/141	1.41 (0.81–2.46)	1.51 (0.84–2.71)
>160	89/145	1.36 (0.78–2.37)	1.32 (0.73–2.38)
Trend *P*		0.26	0.48

[a] Adjusted for age, sex, and center.
[b] Adjusted for age; sex; center; intake of energy, alcohol, fiber, folate, and total fat; number of months between follow-up colonoscopies; smoking status; and aspirin use.

reasons other than high iron stores. First, because high serum ferritin is commonly observed in individuals with high alcohol consumption, liver problems, infection, or inflammation (18, 19), we excluded subjects with any of the following: aspartate aminotransferase >75 or alkaline phosphatase >150; history of chronic pancreatitis, chronic hepatitis, or cancer reported at baseline; or heavy alcohol consumption at baseline, defined as five or more alcoholic beverages a day. In a separate analysis, we excluded people with serum ferritin >161 μg/liter for women or 300 μg/liter for men (20) regardless of the reason for elevation. Results from analyses excluding these patients were not meaningfully different from those based on the full study population. Age was not associated with ferritin concentration in this study population and was not used as a basis for exclusion.

Lastly, for the logistic regression analyses of dietary iron, we used three different measures of iron intake: total iron intake categorized as <10 or ≥10 mg/day, tertiles of energy-adjusted iron intake, and red meat intake in categories corresponding to <2, 2 to <5, and ≥5 servings/week. We ran models stratified on iron store repletion status (≤70, 70 μg/liter), as well as models with ferritin concentration × dietary iron category interaction terms. The number of participants reporting taking iron supplements at baseline ($n = 25$) was too small to permit evaluation of the association of iron supplement use with risk; we did not classify multivitamin supplement users as iron supplement users to avoid confusing a possible effect for supplemental iron with that of other vitamins and minerals.

Results

Ferritin concentrations were determined for 733 (98%) of the 751 patients who completed the clinical trial. Of these patients, 79% were men, and 85% were white. Their ages ranged from 25 to 78 years and averaged 61 years. Differences in alcohol consumption and aspirin use between participants who had an adenoma recurrence and those who did not generally mirrored previously described epidemiological associations (Table 1). There were no substantial differences between cases and controls with regard to cigarette smoking history or mean intake of fat and fiber, but cases tended to have lower intake of iron (Table 1).

The geometric mean serum ferritin concentration was 107.1 μg/liter (95% CI, 95.5–120.1 μg/liter) in cases and 99.1 μg/liter (95% CI, 90.2–108.8 μg/liter) in controls. Serum ferritin concentrations ranged from 4 to 654 μg/liter (geometric mean, 68.1 μg/liter) in women and from 2 to 853 μg/liter (geometric mean, 113.8 μg/liter) in men (Table 2). A lower proportion of women than men had ferritin concentrations >160 μg/liter, and the difference in serum ferritin concentration between cases and controls was more pronounced among women (Table 2).

In a multiple logistic regression model based on 687 patients with complete covariate data, there was no statistically significant linear association between log ferritin concentration and adenoma recurrence ($P = 0.33$). However, patients with serum ferritin concentrations >70 μg/liter had an OR for adenoma recurrence of 1.3 to 1.5 relative to patients with ferritin ≤30 μg/liter (Table 3). Recurrence in patients with ferritin concentration between 31 and 70 μg/liter was similar to those in the lowest category (OR, 1.03; 95% CI, 0.54–1.94). When serum ferritin concentration was dichotomized, the OR for adenoma recurrence was 1.39 (95% CI, 0.96–2.02) for patients with serum ferritin >70 *versus* ≤70 μg/liter. The association between ferritin concentration and adenoma recurrence appeared to be stronger in women than in men (Table 4), but this analysis was based on relatively small numbers, especially in women. The test for sex by ferritin category interaction was not statistically significant ($P = 0.24$).

To assess whether the amount of bioavailable iron consumed in the diet might determine risk more strongly among patients with replete iron stores, we examined associations of various measures of iron intake with adenoma recurrence among subgroups of patients classified as to whether ferritin concentrations were > or ≤70 μg/liter. Although intake of total dietary iron, energy-adjusted iron, and red meat were all inversely associated with risk of adenoma recurrence in patients with replete iron stores, these measures were less consistently related to adenoma recurrence among patients with nonreplete

Table 4 ORs for adenoma recurrence by serum ferritin levels by sex, ferritin dichotomized ($n = 687$)

	Women			Men		
	No. of cases/ noncases	Minimally adjusted OR[a] (95% CI)	Fully adjusted OR[b] (95% CI)	No. of cases/ noncases	Minimally adjusted OR[a] (95% CI)	Fully adjusted OR[b] (95% CI)
Ferritin (μg/liter)						
0–70	19/59	1.0	1.0	53/91	1.0	1.0
>70	28/45	1.95 (0.93–4.09)	2.42 (0.97–6.02)	151/241	1.24 (0.83–1.87)	1.23 (0.80–1.89)
P		0.08	0.06		0.30	0.35

[a] Adjusted for age and center.
[b] Adjusted for age; center; intake of energy, alcohol, fiber, folate, and total fat; number of months between follow-up colonoscopies; smoking status; and aspirin use.

Table 5 ORs by intake of total iron and red meat in those with ferritin concentrations ≤70 and >70 μg/liter

	Ferritin ≤70 μg/liter		Ferritin >70 μg/liter	
	No. of cases/ noncases	Fully adjusted OR[a] (95% CI)	No. of cases/ noncases	Fully adjusted OR[a] (95% CI)
Dietary iron (mg/day)				
<10	23/45	1.0	57/67	1.0
≥10	49/105	0.44 (0.16–1.21)	122/219	0.56 (0.30–1.03)
Energy-adjusted iron				
Tertile 1	32/47	1.0	72/78	1.0
Tertile 2	24/49	1.33 (0.50–3.53)	60/96	0.64 (0.36–1.13)
Tertile 3	16/54	0.65 (0.22–1.91)	47/112	0.44 (0.22–0.84)
Trend *P*		0.29		0.02
Red meat (servings/wk)				
<2	24/59	1.0	52/79	1.0
2–5	30/64	1.08 (0.45–2.60)	80/116	0.95 (0.57–1.58)
>5	18/27	1.34 (0.44–4.12)	46/91	0.58 (0.31–1.09)
Trend *P*		0.61		0.08

[a] Adjusted for age; sex; center; intake of energy, alcohol, fiber, folate, and total fat; number of months between follow-up colonoscopies; smoking status; and aspirin use.

iron stores (Table 5). Nonetheless, *P*s for the ferritin × dietary intake interaction terms were all >0.50 except for the highest category of red meat intake ($P = 0.08$).

Discussion

In this follow-up study, risk of adenoma recurrence was not linearly related to log concentration of serum ferritin. Risk appeared to be moderately increased among patients with ferritin concentrations >70 μg/liter, a point above which iron stores are likely replete. This latter finding, although not statistically significant, seemed more pronounced among women than among men. In patients with serum ferritin concentration >70 μg/liter, in whom iron absorption was presumably minimal, dietary iron was inversely associated with risk; intake of red meat was less clearly associated with risk in patients with serum ferritin concentration ≤70 μg/liter, in whom a higher proportion of dietary iron should be absorbed.

Two prior published reports, both from case-control studies, have evaluated the association between risk of colorectal adenomas and serum ferritin. In one of these reports, based on patients referred for colonoscopy because of suspicion of neoplasia, serum ferritin was strongly associated with an increased risk of adenomas (6). In the other study, based on a true screening population of asymptomatic adults undergoing flexible sigmoidoscopy, serum ferritin was weakly (and not statistically significantly) associated with increased adenoma risk (11). Our findings, based on a group of patients prospectively followed for adenoma recurrence, are consistent with the results from the latter study and indicate that any association between adenomas and iron stores is likely to be relatively modest overall. It is possible, however, that some individuals are more susceptible to the effects of iron stores because of inherited or other unmeasured environmental factors.

Other laboratory measures of iron status have also been examined, and most studies using serum iron and transferrin saturation (7–9), although not all (21), have reported a strong association with invasive cancer risk. Serum ferritin, the primary iron storage protein, is thought to be a more stable and informative indicator of iron stores than other measures (22). A variety of conditions can cause serum ferritin levels to increase without a concomitant increase in iron stores (18, 19), and we lacked detailed information on these conditions. Nevertheless, results from analyses that excluded individuals with elevated ferritin concentrations regardless of underlying cause were not appreciably different from those that included these individuals.

We can offer no explanation, other than the play of chance, as to why the relationship between ferritin and adenoma recurrence appeared to differ between men and women, and we are unaware of any prior finding of differing thresholds for a ferritin effect by sex. Ferritin concentrations were generally higher in men, but our analyses used the same cutpoints for both sexes. Given the relatively older age of our study population, results in women are also unlikely to have been markedly influenced by the inclusion of premenopausal women. The ferritin concentrations observed in this study population are similar to those reported in other studies conducted among older populations (23, 24) and support the notion that differences between men and women in serum ferritin concentrations decrease but do not disappear entirely, even at older ages (25, 26).

Iron in the lumen of the large bowel has been hypothesized to increase colorectal neoplasia, perhaps through DNA damage caused by pro-oxidant hydroxyl radicals formed by the Fenton reaction in the presence of ferrous iron (2). Iron also appears to stimulate proliferation of tumor cells (3, 4), possibly through its role as a rate-limiting nutrient for neoplastic cells (5). A possible effect of iron on tumorigenesis in the colorectum is especially intriguing because colonocytes may be directly exposed to high concentrations of unabsorbed iron in the gut lumen. If the principal effect of iron is to accelerate the transition from adenoma to cancer, then this could also explain the apparently stronger association between iron stores and invasive cancer as opposed to adenoma (6–9). The availability of serum drawn at entry to the study allowed us to assess iron stores at a period when subjects were known to be polyp-free. In consequence, however, our results may pertain only to the earlier phases of the adenoma-carcinoma sequence.

Prior studies of dietary iron and colorectal adenoma (27–32) have produced little support for an increased risk with greater iron intake. In fact, results of most of these studies suggest an inverse relationship between adenoma and iron intake, and in one of these studies (32), as well as in prior analyses from our present population (12), this apparent protective effect of dietary iron was statistically significant and pertained to both women and men. Whereas one report (11) described a positive association between iron intake and adenoma, this result largely related to iron supplements rather than iron from food sources. In our study, too few patients ($n = 25$) reported taking iron supplements at baseline to evaluate its association with risk of recurrence.

The suggestion in our data of a moderately increased risk of adenoma recurrence among persons with ferritin concentrations >70 μg/liter seems paradoxical in view of our finding that dietary iron was inversely associated with adenoma risk in these individuals. We considered iron from dietary sources only rather than total iron from both dietary and supplemental sources. This approach, however, seems an unlikely explanation for the inverse association that we observed because in our prior analyses (12), supplemental iron was only weakly positively associated with adenoma recurrence, and supplement use was slightly inversely associated. An inverse association with dietary iron could reflect consumption of other protective factors correlated with iron in the diet, although the association persisted even after adjustment for intake of fiber and folate (12). It is also possible that chance has contributed to these apparently conflicting observations.

The presence of iron in the colonic lumen is difficult to infer from dietary reports, in part because of variability in absorption of iron from the diet. When iron stores are not replete, serum ferritin is inversely correlated with iron absorption; however, when iron stores are replete, iron absorption appears to be minimal and not strongly related to serum ferritin concentration (15, 33). This finding suggested to us that less dietary iron would reach the colon in patients with low iron stores, and thus the relationship between dietary iron and adenoma risk might differ depending on serum ferritin concentration. In fact, in our data, the inverse association between intake of dietary iron and red meat was more consistent among those with replete iron stores than among those with nonreplete stores.

In addition to iron stores, dietary substances such as phytic acid, which chelates iron and renders it nonreactive (34), and the form of iron (heme or nonheme) also influence iron absorption and add to the difficulty of predicting luminal iron exposure from dietary intake alone. Although we attempted to account for iron bioavailability by examining the effect of red meat in particular, other dietary factors that enhance or inhibit iron bioavailability and absorption were not corrected for in our models because such a correction would require meal-level dietary information (35). However, consumption of vitamin C supplement, tea, and coffee, potentially important factors in iron bioavailability, was similar between cases and controls (13, 36).

In summary, we found no clear relationship between serum ferritin concentration and adenoma recurrence. Replete iron stores, as indicated by serum ferritin concentration >70 μg/liter, were modestly but not statistically significantly associated with increased risk of adenoma recurrence relative to nonreplete stores. Iron intake was inversely associated with adenoma recurrence among those with replete iron stores but was less clearly associated with adenoma recurrence among those whose stores were nonreplete. The results from our analyses seem somewhat paradoxical, and data from other human studies are still too scant to permit a clear assessment of the relationship between iron intake, iron stores, and colorectal tumor risk. Future studies of the role of iron in colorectal cancer development may be enhanced by consideration of the dietary bioavailability and absorption of ingested iron.

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